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Type IV hypersensitivity to vitamin K

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The day after intramuscular injection of vitamin K_1 (phytomenadione) into her thigh, a 27-year-old-woman with normal liver function developed a relapsing and remitting eczematous reaction localized to the injection site, and later a further eczematous reaction under an adhesive dressing (Duoderm®). On patch testing, she was positive to vitamin K_1 and cross-reacted to vitamin K_4; she was also positive to colophonium and to ester gum rosin, the dressing adhesive. Recurrent angioedema persisted for several months and, 2 years later, symptoms were still occurring over the injection sites. Structure-activity relationships among vitamin K allergens are discussed.

Key words: allergic contact dermatitis; menadiol; phytomenadione; vitamin K. © Blackwell Munksgaard, 2002.

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We describe an unusual case of allergy to vitamin K following an intramuscular (i.m.) injection of vitamin K_1 that resulted in a relapsing and remitting localized eczematous reaction.

Case Report

A 27-year-old woman had been diagnosed with cystic fibrosis (CF) at birth when she presented with meconium ileus. She had CF-related diabetes mellitus, which was well controlled with insulin. Liver ultrasound showed coarse echotexture and marked fatty changes, which were consistent with her diagnosis. Liver function tests and international normalized ratio (INR) were normal. Her regular medication included pancreatic enzymes, vitamin A, D and E supplements, prophylactic oral flucloxacillin and nebulized tobramycin. Sputum cultures grew chronic *Pseudomonas aeruginosa*. She attended hospital approximately 2× yearly for treatment of respiratory exacerbations. This was made difficult due to the presence of multiple antibiotic allergies. Prior to dental surgery she received an i.m. injection of vitamin K_1 into her thigh, as a prophylactic measure against subnormal vitamin K levels, which occur in up to 78% of pancreatic-insufficient patients with CF (1). The following day she noticed transient erythema overlying the injection site, which was followed 6 weeks later by localized pain, erythema and oedema. A diagnosis of cellulitis was made and she was started on intravenous (i.v.) cefuroxime. Over the next few days the features became more consistent with localized eczema and 30 mg/day of oral prednisolone was prescribed. Following referral to the dermatology department, treatment with super-potent topical corticosteroids, corticosteroid injections and corticosteroids under occlusion with Duoderm® (ConvaTec, Uxbridge, UK) failed to result in any improvement. She then also developed an eczematous reaction under the Duoderm dressing.

She was patch tested to standard, corticosteroids and medicaments series, together with samples of vitamin K, with the following relevant positive reactions at day 2 (D2) and D4: colophonium 20% petrolatum (pet.) ?+/++, ester gum rosin 20% pet. ++/++ (the adhesive in Duoderm), water-soluble vitamin K_4 (menadiol phosphate) 1% aq. ?+/++, lipid soluble vitamin K_1 2 mg/mL (Konakion®, Roche, Welwyn, Garden City, Herts, UK) –/++ and lipid-soluble vitamin K_1 10 mg/mL without polyethoxylated castor oil (Konakion MM®) –/++. Unfortunately, the pharmaceutical company was unable to supply the separate ingredients of the injections for individual testing. Tests in 20 controls were negative.

Further reactions to fragrance mix 8% pet. ++/++ and Myroxylon Pereirae 25% pet. –/+ were of unknown relevance. Following the week of patch testing the patient developed recurrent angioedema, which persisted for several months and was treated with non-sedating antihistamines. Two years later, she continued to be troubled by recur-

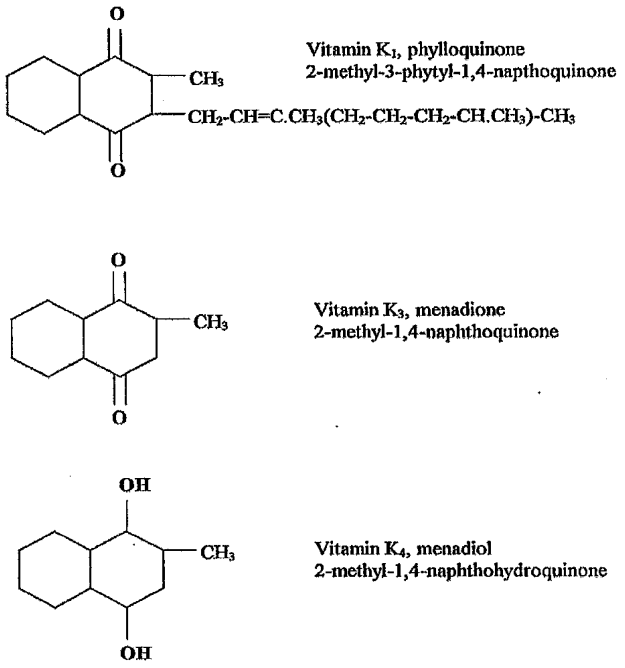

Fig. 1. Structure of vitamin K.

rent symptoms overlying the injection site, despite no further treatment with vitamin K.

Discussion

Vitamin K and its analogues are frequently used in the treatment of hypoprothrombinaemia found in diseases of the liver, biliary tract and small intestine. It is essential for the biosynthesis of prothrombin and factors VII, IX and X in the liver. The natural form of vitamin K_1 is partially absorbed from nutrition, partially synthesized by gut-bacteria. At least three synthetic analogues exist: vitamins K_2 to K_4. The effective part of the K vitamins is the 1,4-naphthoquinone ring, and saturated side-chains determine the differences between the analogues (Fig. 1).

In the UK, vitamin K is currently available in two pharmaceutical preparations. Menadiol sodium diphosphate is a water-soluble vitamin K analogue (tetra-sodium salt of 2-methyl-1,4-naphthohydroquinone diphosphate, vitamin K_4) for oral administration. Konakion ampoules are used for i.m. or i.v. injections. They contain the lipid-soluble 2-methyl-3-phytyl-1,4-naphthoquinone (phytomenadione, vitamin K_1) and also polyethoxylated castor oil as a non-ionic surfactant. Apart from prolonged cutaneous reactions in patients with liver disease, the data sheet lists anaphylactic reactions associated with histamine release in animal studies and also in humans due to the polyethoxylated castor oil. This is not contained in Konakion MM, which is therefore usually suggested as an alternative (2).

The lipid-soluble vitamin K_1 (phytomenadione) causes more cutaneous reactions than its water-soluble analogues. The literature lists two main types of reactions following parenteral injection of vitamin K_1: pruritic erythematous plaques at the injection site 1–2 weeks after the administration of vitamin K_1, resolving within weeks or months, are the more common (3–8). Scleroderma-like lesions have more rarely been described, with or without preceding inflammation (9, 10).

One report described a localized rash in six patients with liver disease 7–16 days following the first vitamin K_1 injection, which spread in four patients and resolved with scaling over 9–22 days. All patients then received watere-soluble vitamin K_4 (menadiol) without problems (9). Fiv patients had intradermal (i.d.) testing with menadiol, Konakion and its individual components (polyethoxylated castor oil, propylene glycol and phenol), and reacted only to the whole preparation (Konakion). This report suggested that only large doses of vitamin K_1, as used in patients with liver disease, produced a reaction, and that this was not immunologically mediated, as lymphocyte transformation tests and leucocyte migration inhibition with vitamin K_1 were unaltered. This was in contrast to most other publications, which have concluded that reactions to vitamin K are due to an immune response.

Initially, cutaneous reactions to vitamin K_1 were mainly reported in patients with liver disease, particularly due to alcohol (7). Finkelstein (5) then described six cases associated with liver disease in primary biliary cirrhosis, chronic myeloid leukaemia, amyloidosis and pre-eclampsia. The local eczematous reactions remained symptomatic for months despite potent topical corticosteroids. The patch and i.d. tests of all patients were negative to water-soluble vitamin K_3 (menadione, 2-methyl-1,4-naphthoquinone). Three patients had positive patch tests to two commercially available lipid-soluble formulations of vitamin K_1. Intra-dermal testing was positive in all four patients in whom it was performed. A Type IV hypersensitivity reaction was the suspected immunological mechanism.

Skin hypersensitivity to vitamin K in patients without liver disease (as in our case) has previously been reported, though less commonly (4, 5).

One patient with hypoprothrombinaemia secondary to hepatitis developed sclerodermatous skin changes 1 year after starting regular vitamin K_1 injections. She was negative on patch testing with vitamin K_1 (as is) and phytomenadione 1%

aq., but was positive on i.d. testing with vitamin K_1, resulting in erythema and induration at D2. One year after discontinuation of treatment, the scleroderma remained unchanged (10).

In all cases described, only the whole preparation of vitamin K_1 (in its vehicle) or vitamin K_1 alone elicited positive patch tests. When individual additives were tested, the results were negative (6–9). However, patch testing may be falsely negative and i.d. tests necessary to exclude the diagnosis completely (6, 7, 10). Patch testing to vitamin K_4 (menadiol) have generally been negative (4, 9).

No previous exposure to vitamin K_1 was required for the development of Type IV hypersensitivity, with primary sensitization occurring within 1–2 weeks (6, 9) or after a longer time period, as in our patient.

Previous reports have suggested that sclerodermatous reactions take longer to resolve than the eczematous reaction. However, eczema has been reported to last for many months to over a year despite all therapeutic efforts (6, 7), and our patient continues to have problems 2 years after the vitamin K_1 injection.

Reports of reactions to water-soluble vitamin K analogues are less common. Vitamin K is absorbed through the skin. Therefore, in 1942, the option of a therapeutic application of vitamin K_3 was investigated (11). This had to be abandoned, as application of vitamin K_3 1% in an ointment base to the skin produced an irritant contact dermatitis. Concentrations of 0.1–0.01% resulted in allergic responses following sensitization (12). Following therapy with oral vitamin K_3 (menadione), one patient developed an exanthem and had repeatedly positive patch tests (13). A 7-week-old breast-fed infant had an urticarial reaction 2 h after oral vitamin K. No further investigations were performed to confirm a causal link (14). A pharmaceutical worker developed a contact eczema and positive patch tests to vitamin K_4 (menadiol) and also cross-reacted to vitamin K_3 (menadione). Patch tests were negative to vitamin K_1 (15).

We describe in this report an unusual patient with normal liver function, who was primarily sensitized after i.m. administration of vitamin K_1 (phytomenadione), resulting in a relapsing and remitting localized eczematous reaction. She cross-reacted to vitamin K_4 (menadiol) on patch testing. It is therefore possible that she reacted to the active 1,4-naphthoquinone ring, rather than to a side-chain, which one suspects instead in the previously reported patients without cross-reactions. The only other report of a cross-reaction is that to the two similar water-soluble analogues vitamins K_3 and K_4 (15).

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